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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/656,309	09/06/2000	Walter Callen	DIVER1350-2	9418

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	**PAPER NUMBER**
1652	18

DATE MAILED: 04/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/656,309	Applicant(s) CALLEN ET AL.	
	Examin r Richard G Hutson	Art Unit 1652	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-42 and 53-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-42 and 53-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment of the specification, amendment of claim 31, cancellation of claim 52 and addition of new claims 53-88, Paper No. 17, 1/22/2003, is acknowledged. Claims 31-42 and 53-88 are at issue and are present for examination.

Applicants' arguments filed on 1/22/2003, Paper No. 17, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-88 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a selection step in which the generated variant is tested or screened such to determine which of the generated variants encode a polypeptide having polymerase activity. Applicants claimed methods would not generate a variant that encodes a polypeptide having polymerase activity without the above omitted step. In fact the majority of species of applicants claimed genus of methods would result in polypeptides which do not have polymerase activity.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-42, 65-76 and 77-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 31-42 and 52, applicants have cancelled claim 52, amended claim 31 and added new claims 53-88 and traverse this rejection as it applies to these new claims. Applicants submit that the function of the claimed method is to generate a variant that encodes a polypeptide having polymerase activity and that the function of the variant is to encode a polypeptide having polymerase activity. Applicants have thus amended the claims to more clearly define the invention.

Applicants submit that the amended claims are drawn to methods of generating a variant encoding a polypeptide having polymerase activity and that applicants have described numerous protocols that can be used to practice the claimed invention. Applicants submit that armed with the disclosure provided by applicants (e.g. the nucleotide sequences that encode for polypeptides having polymerase activity, exemplary protocols and an assay to test for activity) one of ordinary skill in the art could take a sequence having at least 70% identity to a sequence of SEQ ID NO: 1 and

which encodes for a polypeptide having polymerase activity, subject it to one of the exemplary techniques, such as error-prone PCR and produce a variant, which can be expressed and tested for polymerase activity. Thus applicants submit that the specification sufficiently describes the claimed invention so that a skilled artisan would recognize that the inventors were in possession of the claimed invention.

Applicants argument is not found persuasive because while applicants have sufficiently described the claimed methods of generating a variant of SEQ ID NO: 1, applicants have merely described a single species of the genus having 70% identity to SEQ ID NO: 1, and thus applicants description of the claimed methods of generating a variant that encodes a polypeptide having polymerase activity comprising obtaining and modifying a nucleic acid sequence having at least 70% identity to SEQ ID NO: 1 are not sufficient.

As previously discussed, there is no disclosure of any particular structure to function/activity relationship in any disclosed species either used by or generated by such methods. The specification also fails to give guidance as which if any residues should be modified by disclosing any identifying structural characteristics or properties of the SEQ ID NO: 1, and the specification is even more deficient in its guidance necessary for the proposed methods of modifying variant polynucleotides having a mere 70% identity to SEQ ID NO: 1. Thus there is no predictability of the claimed methods of modifying molecules which are as yet to themselves be described. Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact

terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Newly added claims 65-88 are included in this rejection for the same reasons that claims 31-42 are rejected as discussed above.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 65-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating a polymerase variant: comprising obtaining a nucleic acid comprising SEQ ID NO:1 and sequences complementary thereto and modifying, deleting or adding one or more nucleotides in said sequence, wherein said variant maintains polymerase activity, does not reasonably provide enablement for any method of generating any variant: comprising obtaining a nucleic acid comprising obtaining a nucleic acid sequence comprising a fragment of at least 30 consecutive nucleotides of a sequence having at least 70% identity to the sequence set forth in SEQ ID NO: 1 and encoding a polypeptide having polymerase activity or its complement and modifying, deleting or adding one or more nucleotides in said sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 65-88 are so broad as to encompass any method of generating any variant that encodes a polypeptide having polymerase activity comprising obtaining a nucleic acid sequence comprising a fragment of at least 30 consecutive nucleotides of SEQ ID NO: 1 or a fragment of at least 30 consecutive nucleotides of a sequence having at least 70% identity to the sequence set forth in SEQ ID NO: 1 and encoding a polypeptide having polymerase activity or its complement and modifying, deleting or adding one or more nucleotides in said sequence to generate a variant that encodes a polypeptide having polymerase activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims, including all methods of generating variant polynucleotides which encode enzymes with polymerase activity wherein said variant polynucleotide is a variant of any polynucleotide comprising a fragment of at least 30 nucleotides of SEQ ID NO: 1 or comprising a fragment of at least 30 nucleotides of a sequence that is at least 70% identical to SEQ ID NO: 1.

The claims rejected under this section of U.S.C. 112, first paragraph, do not place minimal structural or functional limits generated variants. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is gives no guidance beyond the structure of SEQ ID NO: 1 as to how one would obtain and/or modify the polynucleotide of SEQ ID NO: 1 such that the variant generated encoded a protein which had polymerase activity.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all methods of modifications of any nucleic acid sequence having 30 consecutive nucleotides of SEQ ID NO: 1 or those nucleic acids at least 70% identity to

SEQ ID NO: 1, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting function/activity; (B) the general tolerance of SEQ ID NO: 1 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleic acid residue of SEQ ID NO: 1 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to generate desired variant and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those methods of the claimed genus having the desired function.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any method of generating any variant: comprising obtaining a nucleic acid having 30 consecutive nucleotides of SEQ ID NO: 1 or those nucleic acids at least 70% identity to SEQ ID NO: 1, and modifying, deleting or adding one or more nucleotides in said sequence. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired

biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants amendment of previously rejected claims 31-42 based on a lack of enablement and traversal based on this amendment is noted. Claims 31-42 have been withdrawn from this rejection based on applicants amendment and traversal.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Primary Patent Examiner
Art Unit 1652
April 10, 2003